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ABSTRACT

Environmental influences can significantly affect (both positively and negatively) the developing child. Three ways in which the environment affects the developing organism are induction, facilitation, and maintenance. In the case of induction the presence or absence of specific stimuli totally determines whether or not a particular developmental event occurs, such as sexual differentiation. Facilitation is apparent when the rate and/or maximal level of maturation is altered, as in the case of the influence of thyroid hormone on the rate of cell division. The term maintenance refers to the presence of any environmental factors necessary for the preservation of an already developed state. Alternately, and in particular reference to human development, certain aspects of the environment, such as toxic compounds, heavy metals, pesticides, food additives, and parental drug abuse may have predominately negative effects on the developing child. Although every part of the developing organism is subject to this environmental influence, in recent years considerable emphasis has been placed on the developing nervous system. As a result of scientific investigations, significant advances have been made toward understanding the consequences of toxic exposure. Future research should increasingly emphasize basic research approaches designed to reveal how toxicants produce their effects. In addition, special attention must be given to the developing organism in any assessment of the consequences of neurotoxic compounds. (Author/RH)

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MATRIX NO. 16

ENVIRONMENTAL EFFECTS ON HEALTH WITH SPECIAL EMPHASIS ON NEUROTOXICOLOGY

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WITH SPECIAL EMPHASIS ON NEUROTOXICOLOGY

Environmental influences on child health begin at conception and continue throughout postnatal development. Such influences (positive and negative) significantly affect immediate and future adaptation. Gottlieb (1976) has categorized three ways in which the environment affects the developing organism. These are induction, facilitation, and maintenance.

Induction is the most dramatic (and also least documented). In such a situation, the presence or absence of specific stimuli totally determines whether or not a particular developmental event occurs. When the inducing stimuli occur at the appropriate point in development, such stimuli exert positive value. On the other hand, interference with the appropriate stimuli potentially leads to deleterious influences on child health. Except for the role of gonadal hormones in the process of sexual differentiation (Whitsett & Vandenbergh, 1978), firm evidence for inducing stimuli is difficult to obtain.

It is recognized now that sexual differentiation in mammals results from the presence of appropriate hormonal stimuli during precise points in development. Differentiating events occur at the genetic, morphological, and neural levels and are separated across chronological age. Genetic sex is determined at the time of conception and is dependent on the chromosomal constitution of the fertilized ovum. Gonadal and neural differentiation, however, do not occur until much later in development. Morphologic development of males and females develop similarly with the potential for differentiation as either sex. In the absence of hormonal signals, genitalia of the female develop, but in the presence of appropriate stimuli, male genitalia develop. At an even later point in development, sexual differentiation of the nervous system occurs. In the absence of hormonal signals, the nervous system proceeds to develop in a female-like fashion, so that in adulthood, the potential for cyclic fluctuations in gonadal and pituitary hormones typical of the female reproductive cycle occur. If, however, hormones (e.g., estrogens) are present, an acyclic nervous system characteristic of the male develops. The inducing hormone for male-like nervous system differentiation appears to be estrogen which enters the brain as testosterone and thereafter is converted to estrogens.

Because sexual differentiation occurs in at least three separate stages, it is possible for genetic males to develop as morphological females or vice versa and for morphological and neural sex to be disconcordant. The fetal androgenization syndrome readily demonstrates the importance of an appropriate maternal environment for the development of the fetus. In this situation, the mother is deficient in adrenal corticosteroids and, therefore, the appropriate negative feedback systems to the pituitary are inoperative. As a consequence, overproduction of other adrenal steroids (of which estrogen and progesterone are included) occurs and male-like differentiation of the fetus takes place.

Since many environmental stimuli (e.g., noise, crowding, etc.) may be stressful to the mother, chronic elevation of adrenal secretions is a potential source of interference with appropriate inducing stimuli for sexual differentiation (Joffe, 1978).

Furthermore, environmental pollutants, such as DDT, Kepone, lead, etc., also may affect sexual differentiation. Both DDT and Kepone appear to exert a mild estrogenicity, and Kepone exerts clear masculinizing effects on females when administered neonatally during the critical period for neural sexual differentiation (Gellert, 1978).

Facilitation is apparent not when the environmental stimuli influence whether or not a particular event will occur, but when the rate and/or maximal level of maturation is altered. Notable examples of facilitation include the effect of thyroid hormone on the rate of cell division and migration and the role of visual and/or auditory stimuli in the functioning of the respective sensory systems. For most developmental processes, the appropriate timing of events is an integral aspect of the final organized functioning unit. However, if the timing of development is shifted, the final product may be changed dramatically. For example, the development of cells in the cerebellum occurs in a synchronized fashion. Purkinje cells develop rather early, but do not undergo their final developmental events until they are stimulated by another cell population, the migrating granule cells. These cells develop in the external granule cell layer and, as they migrate inward to their final location in the internal granule layer, they stimulate the waiting Purkinje cells to complete their maturation process. Too much or too little thyroxine drastically alters the time at which the granule cells migrate and, as a consequence, disrupt the entire organization of the cerebellar circuitry and its dependent motor coordination (Nicholson & Altman, 1972).

Clearly, many external environmental events accelerate the organism's ability to adapt to environmental challenges. Thus, early experience with *stress* leads to the development of an organism better able to adapt to novel stimuli (Levine, 1962), and environmental enrichment facilitates acquisition of maze skills (Rosenzweig & Bennett, 1978). Similarly, proper development of the mammalian sensory systems requires an appropriate balance in sensory input (Brenowitz *et al.*, 1980). For most environmental stimuli, there is an optimal range, compatible with *healthy* development. Outside this range, however, appropriate adaptation may be stunted. Many factors that are beneficial at some level, in sufficient quantity, may have disruptive influences on child health. For example, while developing infants require sensory stimuli for the attainment of proper functioning of the sensory apparatus, overstimulation, stress, crowding, and noise pollution may increase sensory stimuli above the optimal level. As a consequence, the infant may respond by irritability, hyperexcitability, or even withdrawal. The appropriate configuration of environmental stimuli, therefore, is very important for child development.

Maintenance is the least dramatic (although possibly the most evident) effect of the environment. In this case, the environment does not influence whether or not, or how much or how soon; instead, the presence of the environmental factor is necessary for the preservation of an already developed state.

For some aspects of the environment, there is no particular beneficial effect on the developing individual. A decade ago, the number of environmental compounds known (or even suspected) to produce deleterious influences on human health were relatively few. Over the past 10 years, this number has multiplied significantly and,

with continuing investigation, the number is bound to increase. For many compounds, their potential health hazard is discovered during routine investigation before marketing to the general public. For others, however, the recognition of their toxicity has occurred only after the consequences of widespread contamination. Incidents described below represent cases in which the potential health hazard was not fully recognized prior to the manifestation of toxicity in a human population, and demonstrate the necessity of identifying early symptoms of toxicity.

In early 1975, an outbreak of Kepone intoxication occurred in a factory in Hopewell, Virginia. Kepone is the commercial name for chlordecone, which since its introduction in 1953, has proved to be a highly effective pesticide. In 1975, many factory workers received an acute, high level exposure to the compound, and various neurological symptoms developed. Affected individuals gradually developed tremors which their co-workers termed the "Kepone-shakes" and exhibited reproductive difficulties that brought them to the attention of physicians. As a consequence of the severe symptoms of Kepone toxicity, the pesticide now has been banned in the United States. However, Kepone from the plant contaminated the James River and exerted considerable economic impact on marine life (Taylor *et al.*, 1979). Since the compound is resistant to degradation, it continues to pollute affected areas.

In 1975, Shuman *et al.* (1975) carefully documented the correlation between bathing infants in hexachlorophene and the presence of neural disruption, as well as muscle, urinary, cardiovascular, and other anomalies. These investigations were responsible for the discontinued use of hexachlorophene in household products.

A tragic outbreak of polybrominated biphenyl (PBB) poisoning occurred in Michigan, in 1973. A fire-retardant that contained PBB was included mistakenly in a shipment of animal food additive. The PBB was mixed with the animal food and shipped throughout the state of Michigan. In addition to the loss of 30,000 cattle and other farm animals, farmers and other residents became seriously ill (Schaumburg & Spencer, 1980). Developmental consequences of this exposure are unknown.

During the past 10 years, a significant effort has been devoted to the development of sensitive methods for identifying potential toxicants and for the early detection of symptoms. Tests have been devised for the identification of potentially carcinogenic compounds; use of tissue cultures have been advanced for the prediction of toxicity, and complex biochemical and behavioral regimens have been instituted for the identification of subtle manifestations of low level exposure to toxic compounds. Methods utilized in toxicological research span the entire scientific arena uniting such diverse disciplines as molecular biology, physiology, biochemistry, pharmacology, and psychology.

The immature organism is at a particularly high risk for many environmental substances (e.g., heavy metals, pesticides, food additives) that exist in the parental environment. Compounds, which in the adult organism only temporarily disrupt the maintenance of an already established biological function, may, in the developing organism, totally prevent the function from fully developing and thereby alter the entire process of development. The previously mentioned consequences of inappropriate hormone levels during development are excellent examples. Furthermore, *in utero,* the fetus may be disturbed as a consequence of maternal use of alcohol,

nicotine, caffeine, or other abused drugs. Even hyperthermia, caused by excessive sauna use, has been suggested to have teratogenic potential (Layde *et al.*, 1980), and the inclusion of blighted potatoes in the diet has been correlated with birth defects (Renwick, 1972), although data are not conclusive (Emanuel & Sever, 1973; Masterson, *et al.*, 1974; Mun *et al.*, 1975). It is not likely that the risk to child health can be eliminated completely. However, with appropriate research investigations and the establishment of preventative measures, the number of potential toxicants may be reduced, so that danger to the developing organism can be minimized.

To reach maturity, the conceptus must undergo complex biochemical and morphological changes. During the first stage (the predifferentiation stage), damage to the developing organism is usually all or none. Either all cells die and no embryo is formed, or a few cells survive and produce a normal embryo. During the second (embryonic) stage, however, severe malformations can result from exposure to environmental compounds. It is during this period that the proliferating cells begin to formulate organs and the embryo may be highly sensitive to environmental pollutants. Since different organs mature at different rates, the same compound may affect a variety of organs depending upon the time and duration of exposure. In the third (fetal) stage, the probability of gross malformation decreases since organs reach a period of marked differentiation. However, some structures, such as the nervous system, remain highly susceptible to teratogenic compounds until late pregnancy or even during the postnatal period. Because of the relatively late maturation of the nervous system and the synchrony of neuronal development, even transient exposure to an environmental toxicant may have severe influences on the nervous system. Entire populations of neuronal elements may be eliminated, while others (that already have differentiated) may be relatively untouched. However, because of the missing elements, the organization of the nervous system and its consequent functioning are severely disturbed.

A consideration of the special vulnerability of developing children must include *in utero* exposure to drugs and particularly drugs of abuse. Although it has been recognized that alcohol has teratogenic potential, only in the past decade has public attention been paid to the Fetal Alcohol Syndrome. In 1973, Jones and colleagues (Jones *et al.*, 1973) described a common pattern of physical abnormalities in individuals whose mothers had abused alcohol during pregnancy. Since that time, hundreds of reports of Fetal Alcohol Syndrome have appeared, and the prevalence in the population of partial expression of the syndrome is estimated to be about 3 to 5 live births per thousand (Clarren & Smith, 1978). Fetal Alcohol Syndrome consists of at least three characteristics: growth deficits (body weight and length); distinctive facial characteristics; and indications of central nervous system dysfunction. Neural disturbances range from mild to moderate mental retardation, with poor coordination, neonatal irritability, and hyperactivity in childhood (Morrissey & Mottet, 1980).

Within the clinical setting, evaluation of the consequences of prenatal exposure to any compound is extremely difficult. Mothers who abuse alcohol also may abuse cigarettes, other drugs, or may lack proper nutrition. Identification, assessment, and investigation of the effects of prenatal exposure to compounds require, therefore,

the establishment of an appropriate animal model. In the laboratory, higher mortality rates occur in offspring of animals receiving high concentrations of alcohol (Riley, 1979) and malformations may result (Chernoff, 1977; Kronick, 1976; Morrissey & Mottet, 1980). Perhaps of equal importance to the quality of child health are the behavioral effects of alcohol exposure in the absence of physical signs of abnormality (Riley, 1979). Prenatal exposure produces response inhibition in animals and a propensity toward preservation of behavior, which resemble the human symptoms of shorter attention spans and periods of inattentiveness. Biochemical manifestations of alcohol exposure include abnormal patterns of cellular proliferation and a disruption of CNS organization (Banerjee *et al.*, 1978; Ellingboe, 1978).

Possibly the best documented example of a toxic neuronopathy is that produced by methyl mercury (Reuhl & Chang, 1979). While the toxic effects of mercury and its compounds have been recognized for centuries, they were not recognized as significant environmental health hazards until the massive outbreak of hundreds of human cases of mercury poisoning in Minamata Bay and the Niigata District of Japan in the 1950s, and the more recent outbreak of methylmercury poisoning in Iraq during the winter of 1971-1972. The clinical symptoms of methylmercury poisoning include sensory disturbances and cerebellar ataxis, with complaints of tingling and paresthesia in the fingers followed later by numbness. Cerebral and cerebellar atrophy, the major pathological findings of mercurial victims, was consistent with its action as a neuronopathic agent. However, the fetus also had a high vulnerability toward methylmercury toxicity. With low level, prolonged exposure, disruptions of development were severe, with exposed individuals displaying evidence of the decortication syndrome. In the most severe cases, all layers of the cerebral cortex were spongy as a result of complete loss of neurons. With less prolonged exposure, the severity of the symptoms was reduced, but motor defects, mental disturbances, decreased alertness, and changes in emotional state occurred. At the present time, it appears that the amount of physical and mental recovery made by the victims of fetal exposure will be very slight.

As a result of scientific investigations, significant advances have been made toward understanding the consequences of toxic exposure. The number of infant deaths and fetal malformations has decreased. As a consequence of educational campaigns devoted to reducing the prevalence of pregnant females ingesting large quantities of socially acceptable drugs, risks to the developing organism have declined. Furthermore, increased knowledge about the vulnerability of the fetus has eliminated the routine prescription of potentially dangerous compounds to pregnant individuals. The environmental risk to the developing fetus consequently has been reduced substantially during the past decade.

Emergence from the womb, however, does not present the infant with a safe and secure habitat. In particular, the continued maturation and organization of the nervous system postnatally place the infant at special risk for a variety of neurotoxicants. Children are more likely to ingest toxic substances and, once ingested, children often exhibit a low ability to metabolize the compounds. Furthermore, because of the immaturity of the blood-brain barrier, the CNS of children may receive especially high concentrations of ingested materials. Environmental pol-

lutants, therefore, may exert severe, and often fatal, influences on the developing organism.

Lead poisoning is perhaps the best known example of an environmental toxicant for which children are at particularly high risk. Humans carry a greater lead burden than they do for any of the other heavy metals (Morrissey & Mottet, 1980), and within similar environmental conditions, children have higher blood levels than adults (EPA, 1977). Because children indiscriminately ingest various substances, children living in urban environments (especially in older houses in which lead paint or plaster are peeling and easily accessible), are at high risk to lead intoxication. Emission of lead via automobile exhaust or industrial practice also constitutes a threat and particularly is prevalent in city dwellings. In addition, children appear to have an enhanced rate of lead absorption increasing the proportion of ingested material available for organismic damage (Krigman *et al.*, 1980).

Clinical symptoms recognized as a consequence of lead intoxication have been known since the time of Hippocrates (Waldron, 1966). Since lead crosses the placenta (Barltrop, 1969), exposure of pregnant females to high levels of lead may cause abortion of the fetus (Wilson, 1977). Less severe exposure results in encephalopathy or mental retardation (Barltrop, 1969). Even when such severe anomalies are absent, affected children may develop hyperactivity and convulsions (Krigman *et al.*, 1980). It is becoming increasingly evident that low levels of lead exposure to the fetus and infant can result in mental handicap ranging from minimal brain damage to severe mental anomalies. Lead poisoning also has been implicated in a variety of neurological diseases, including motor neuron disease (Campbell *et al.*, 1970), presenile dementia of Alzheimer-type changes (Niklowitz & Mandybur, 1975), diffuse demyelination of the cerebral white matter (Verhaart, 1942), and brain tumors in children (Schreier *et al.*, 1977). In animal studies, it has been suggested that lead during pre- and/or postnatal development delays the maturation of the nervous system (Carpenter & Fern, 1977; Gilani, 1973; Press, 1977; Reiter *et al.*, 1975), with the brain region affected dependent upon the age of exposure.

Although the precise mechanisms of lead intoxication still are unknown, during the last decade significant progress has been made in studying the compound. A variety of behavioral, neurophysiological, neurochemical, neuropharmacological, and neuromorphological studies has been performed in laboratory animals. These studies have suggested that lead binds to sulfhydryl groups or competitively replaces divalent ions such as calcium. Effects of lead on enzyme activity and membrane function are documented (Krigman *et al.*, 1980) and effects of lead on mitochondrial respiration (Holtzman *et al.*, 1978) and impairment of estrogen and progesterone secretion have been reported (Wide & Nilsson, 1977). Lead inhibits adenyl cyclase activity and affects neurotransmitter activity (Kostial & Vouk, 1957; Manalis & Cooper, 1973; Shih & Hanin, 1978).

From the available data, the risk to child health from lead exposure appears to be caused by multiple factors and differs as a function of the time of exposure of the developing individual. Since lead exerts multiple cellular actions, the significance of the exposure depends upon the dynamics of the developing organism and the importance of particular disrupting events to further maturation. It is important,

therefore, that the studies of lead toxicity be compared intimately to those of normal development. Otherwise, the repercussions of lead exposure to child health (and consequent therapeutic measures) will be difficult to evaluate.

In spite of the fact that the precise mechanisms of lead intoxication are still unknown, recognition of the dangers of lead to the child has become widespread. The incidence of accidental exposure has decreased. Media campaigns and educational programs have emphasized the importance of protecting children from lead contaminated paint and plaster, and the lead burden has declined with the requirement that new automobiles use unleaded fuel (Morrissey & Mottet, 1980). Chelation therapy and modern recognitions of the dangers of lead intoxication have reduced the mortality from childhood lead encephalopathy. However, the morbidity of acute lead encephalopathy remains high and the risk of minimal brain damage is still apparent.

The initial necessity for a response to the problems of lead toxicity required immediate action and the development of rapid therapeutic procedures. These procedures, while relatively effective in reducing death and gross manifestations of lead toxicity, have been less successful in dealing with the subtle manifestations of low level exposure to the compound. With the initial problem attenuated, considerably more basic research must be applied to the study of the mode of action of lead on the nervous system and the consequent reduction in the quality of child health.

Pesticides constitute another category of environmental toxicants to which children are likely to be exposed. Among these compounds, the organophosphorus compounds and the polychlorinated compounds have received the most extensive investigation. In neither case, however, have significant clinical findings been reported in children, and most studies have not compared neonate and adult toxicity. Yet, biochemical studies suggest that the pattern of symptoms following exposure is not the same in the young and in the adult. These compounds exert significant influences on the reproductive system of exposed adults (Eroschenko & Wilson, 1975) and in young animals affect sexual differentiation (Gellert, 1978). In a recent study, Kepone was administered to neonatal rats on day 4 postnatal (within the period of sexual differentiation); female neonates exhibited precocious puberty and reproductive failure in adulthood (Gellert, 1978). These studies suggest that the long-term consequences of childhood exposure to pesticides have not been fully realized. In the case of Kepone, which appears to exert estrogenic action on the reproductive system (Palmiter & Mulvihill, 1978), there is every reason to suspect that the process of sexual differentiation may be disturbed. Even though the burden of Kepone in the environment is not increasing, developing children still may be at risk, since Kepone is not readily degradable. In addition, other pesticides still in use may constitute a similar risk.

The role of nutrition in child health is so widespread that it is the subject of popular publications and mass media coverage. Food additives exert deleterious influences on child behavior leading to hyperactivity (Connors, 1980) antisocial behavior, muscle incoordination, and cognitive and perceptual difficulties (Feingold, 1979). Alteration of the diet has been claimed to be an effective therapy in a substantial portion of the cases (Connors, 1980). The proof of these claims is subject to dispute

and will prompt considerable research in the future. Study of the mechanisms of action of food dyes is relatively recent, but dyes have been reported to disturb neurotransmitter accumulation (Logan & Swanson, 1979), to alter membrane permeability of neurons and to alter the ability of the nerve to generate action potentials (Levitan, 1979). Because of their prevalence in the human diet, food additives should continue to be a major topic of research interest.

Of recent concern is the widespread use of flavor-enhancing substances, such as glutamate and aspartate as food additives (Olney, 1980). These compounds belong to a class of substances known to exert excitatory effects on the CNS. Unlike a variety of synthetic materials, these naturally-occurring compounds lead to relatively specific patterns of neuronal cell death. The dangers of widespread use of such compounds recently has been reviewed by Olney (1980), who noted that the compounds often act additively. On the other hand, federal control of the use of these substances considers them in isolation from each other and from the remainder of the diet. Such excitatoxins are common additives in baby food, in some soda pop, and in commercial soup, etc. The market is one heavily biased toward child consumption. Since the combination of various excitatoxins may far exceed the neurotoxic effects of the compounds taken singly, it is imperative that the evaluation of these compounds consider the total diet of the child. Baby food may be safe, but baby food plus soda pop may not.

In summary, during the past decade, significant progress has been made toward the identification and description of toxic substances. Although awareness of the contribution of environmental factors to human health has escalated during the past two decades, research is still in its infancy. A large portion of the laboratory research has been performed on the adult organism. Those studies that have included gestational and/or neonatal exposure have been relatively consistent (even across a wide variety of types of toxicants) in pointing out that the developing organism does not respond to toxicants in the same manner that the adult organism responds.

Because of the immediate concern for treatment of affected individuals and the reduction of the threat from the environment, a large amount of past research has had to be primarily descriptive in nature. These studies have been excellent, and now it is possible to categorize a variety of compounds according to symptoms, site of lesion, and occasionally, even mode of action. However, mechanistic studies (e.g., search for the mechanisms of action of the toxicants) have had to take a backseat to the more descriptive endeavors. In the next decade, increased emphasis must be placed on basic research approaches to the study of toxicants.

Finally, considerable emphasis during the past decade has been placed on the description and study of compounds that produce relatively long-term, severe malformations and/or loss of function. These studies have been invaluable because they, in fact, have been the impetus for the removal of many compounds from the environment. However, while decreasing the risk of compounds in the environment is of great importance, it is of lesser value to those individuals already affected or to whom low level risk remains imminent. Effective therapy for those individuals requires an understanding of the modes of action of the toxic compounds. Particularly

where the developing population is concerned, the ability to evaluate the risk to low level exposure to toxic compounds requires an understanding of the developmental events with which the toxic compound interferes.

Recommendations for increased emphasis in the future should take the following into consideration. Because of the obvious necessity of reducing environmentally-induced deaths and gross malformations, past research has concentrated on agents with relatively severe effects on child health. As the incidence of infant deaths has been reduced, however, it is now time to increase emphasis on those environmental factors that reduce the quality of life. Cultural and environmental traumas, which are of relatively recent origin, challenge the individual's capacity for adaptation. Over the past century, individuals have grouped closer and closer together, leading to increased crowding and consequent increase in density of environmental pollutants. Furthermore, relatively low level exposure to a variety of compounds faces the infant each day of its life. The total number of environmental challenges to which the average child must cope continues to escalate. Past research has concentrated primarily on the impact of individual environmental factors without attention to the fact that children develop in the presence of many potentially deleterious environmental influences. The combination of these factors must be given further investigation. It is possible, even probable, that certain environmental situations may reduce the individual's effectiveness in meeting environmental challenges. Others may exert beneficial influences. Since it is unlikely that we can remove completely environmental pollutants from the child's world, we must consider seriously the modification of his/her lifestyle to reduce the impact of the toxicant.

The past decade has placed heavy emphasis on the adult population, but it is evident that increasing attention to the child population is required. Toxicologists must draw from research in embryology, developmental neurobiology, and developmental psychology to obtain basic information on the principles of development that make the young especially susceptible to environmental factors.

Finally, the past decade has witnessed primarily the emergence of a descriptive science, and it has not yet been possible to synthesize the rapidly accumulating data. What are the factors that are important in predicting the relative sensitivity of the young and adults to particular toxic compounds? Are there structural similarities about toxic compounds that enable us to predict their effects on human health? Can compounds be grouped according to the system and/or molecular action with which they interact? Identifications of the mechanism of action of multiple compounds are essential before such general principles will emerge. However, once a skeleton of such principles is formed, the evaluation of additional compounds can proceed at exponential rates.

Summary

The environment is an essential aspect of the individual's development. Its contribution may be positively providing appropriate stimuli necessary for organismic development. On the other hand, certain aspects of the environment may have predominantly negative effects. Although every part of the developing organism is subject to this environmental influence, in recent years considerable emphasis has

been placed on the developing nervous system. In another paper, several neurotoxicants, which have been identified and investigated during the past 10 years, have been overviewed. For each of these compounds, both the developing individual and the adult can experience long-term consequences of neurotoxicant exposure. However, for many compounds, the consequences of neurotoxicants are not the same in the neonate and adult organisms. Consequently, special attention must be paid to the study of the developing organism in any assessment of the consequences of neurotoxic compounds.

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